CHAPTER 13

Neuroimaging Studies in PTSD

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The prevalence of posttraumatic stress disorder (PTSD) is estimated to be between 8% and 9% (Breslau, Davis, Andreski, & Peterson, 1991; Kendler et al., 1995), with rates of PTSD approximately twice as high in females as they are in males (Breslau, Davis, Andreski, Peterson, & Schultz, 1997). PTSD is often a chronic and recurring disorder (Ballenger et al., 2000; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) and is associated with high rates of comorbid depression and substance abuse (Giaconia et al., 1995; Marshall et al., 2001; Oquendo et al., 2003). The co-occurrence of these disorders is associated with a worse prognosis (Breslau et al., 1997) and greater risk for suicidality (Giaconia et al., 1995; Oquendo et al., 2003).

Preclinical (e.g. animal) studies of the effects of stress have provided a valuable heuristic for generating hypotheses about the brain structures and neural circuits implicated in the pathophysiology of PTSD and for understanding the high rates of comorbidity observed in patients with this disorder. In this chapter, the first section reviews extant neuroimaging studies: the second section highlights relevant preclinical research; and the last section delineates directions for future investigations.

STRUCTURAL NEUROIMAGING STUDIES OF ADULTS WITH PTSD

Table 13.1 summarizes the methods and results of structural neuroimaging studies in adults with PTSD. There have been 11 studies to date, approximately evenly divided between investigating male and female participants.

TABLE 13.1. Structural MRI Studies in Adults with PTSD

Citation	Sample	Lifetime diagnoses	Trauma	Method	Results
Bremner et al. (1995)	26 PTSD (100% M) 22 NC	68% MDD 76% ALC	Combat	MRI (1.5 T), 3-mm contiguous slices	PTSD < NC R hippocampus (8% reduction)
Gurvits et al. (1996)	7 PTSD (100% M) 7 TC 8 NC	57% MDD 71% ALC	Combat	MRI (1.5 T), 3-mm contiguous slices	PTSD = TC > NC subarachnoidal CSF PTSD < TC = NC L/R hippocampus (26%)
Bremner et al. (1997)	17 PTSD (71% M) 17 NC	86% MDD 71% ALC	Child abuse	MRI (1.5 T), 3-mm contiguous slices	PTSD < NC L hippocampus (12%) PTSD < NC L amygdala (trend only)
Stein et al. (1997)	21 CSA (71% PTSD) 21 NC (100% F)	29% MDD NR ALC[a]	Child abuse	MRI (1.5 T), 4-mm slice, 0.4-mm increments	CSA < NC L hippocampus (5%)
Driessen et al. (2000)	21 BPD (57% PTSD) 21 NC (100% F)	NR MDD[b] NR ALC[c]	Child abuse	MRI (1.5 T), 1.25-mm contiguous slices	BPD+PTSD = BPD-no PTSD < NC L/R hippocampus (16%) BPD+PTSD = BPD-no PTSD < NC L/R amygdala (8%)
Bonne et al. (2001)	10 PTSD (70% F) 27 TC	0% MDD 0% ALC	Mixed[d]	MRI (2.0 T), 1.5-mm contiguous slices, 1 wk and 6 mo posttrauma	PTSD = TC hippocampus, amygdala (1-week assessment) PTSD = TC hippocampus, amygdala (6-month assessment)

Schuff et al. (2001)	18 PTSD (100% M) 19 NC	55% MDD NR ALC[f]	Combat	MRI (1.5 T), 3-mm contiguous slices	PTSD = NC hippocampus PTSD = NC entorhinal cortex
Villarreal et al. (2002)	12 PTSD (83%F) 10 NC	100% MDD 8% ALC	Mixed[e]	MRI (1.5 T), 1.5-mm contiguous slices	PTSD < NC L/R hippocampus (13%, 10%) PTSD < NC white matter/intracranial volume PTSD > NC CSF/intracranial volume
Fennema-Notestine et al. (2002)	11 PTSD (100% F) 11 TC 17 NC	NR MDD[g] NR ALC[h]	Partner violence	MRI (1.5 T), 1.2-mm contiguous slices	PTSD = TC < NC WBV[i], cortical gray, frontal gray, occipital gray, medial temporal lobe gray PTSD = TC = NC hippocampus
Vythilingam et al. (2002)	21 MDD/CA (66% PTSD) 11 MDD—no abuse 14 NC (100% F)	43% ALC (MDD/CA) 27% ALC (MDD/NA)	Child abuse	MRI (1.5 T), 1.5-mm contiguous slices	MDD/CA < MDD – no abuse = NC no abuse L hippocampus (15%)
Gilbertson et al. (2002)	Ex+/Ex- Twins (100% M) 12 Ex+PTSD/Ex- Twins 23 Ex+NoPTSD/Ex- Twins	82%/47% ALC (PTSD) 43%/30% ALC (noPTSD)	Combat	MRI (1.5 T)	Ex+PTSD = Ex- Co-Twin < Ex+NoPTSD = Ex- Co-Twin L/R Hippocampus (4%; 10%)

Notes. PTSD, posttraumatic stress disorder; NC, normal control; TC, trauma control; M, male; F, female; MDD, major depressive disorder; CSA, child sexual abuse; BPD, borderline personality disorder; CA, child abuse; ER, emergency room; WBV, whole brain volume; MTL, mesotemporal lobe; L, left; R, right

[a] CSA > NC on lifetime alcohol use measure. No lifetime alcohol abuse diagnoses reported.

[b] BPD > NC on current depressive symptomatology measure. No lifetime depression diagnoses reported.

[c] BPD > NC on lifetime alcohol use measure. No lifetime alcohol abuse diagnoses reported.

[d] Miscellaneous traumas in adulthood requiring treatment at a hospital emergency room.

[e] Half the participants had a history of child physical and/or sexual abuse; the remaining participants had PTSD secondary to assault, rape, accident, or combat.

[f] Inclusion criteria required individuals with history of alcohol dependence to be abstinent for 5 or more years. Investigator unable to recruit PTSD sample without history of alcohol dependence.

[g] PTSD > TC > NC on rating of current depressive symptomatology. No lifetime depression diagnoses reported.

[h] PTSD = NX > TC on alcohol use in past year. No lifetime alcohol abuse diagnoses reported.

[i] WBV computed using supratentorial cranial vault, a measure of cerebrum and cerebrospinal fluid.

Seven of the 11 studies reported reduced hippocampal volume in patients with PTSD compared with normal controls (Bremner et al., 1995; Bremner, Randall, et al., 1997; Driessen et al., 2000; Gurvits et al., 1996; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Villarreal et al., 2002; Vythilingam et al., 2002). There are no clear laterality findings across these seven studies, with three studies reporting reduced hippocampal volume only on the left side (Bremner, Randall, et al., 1997; Stein et al., 1997; Vythilingam et al., 2002), one study reporting reduced hippocampal volume only on the right side (Bremner et al., 1995), and three studies reporting reduced hippocampal volume on both sides of the brain (Driessen et al., 2000; Gurvits et al., 1996; Villarreal et al., 2002). All the individuals in the studies who reported reduced hippocampal volume had high rates of lifetime diagnoses of major depressive disorder (MDD) and alcohol dependence, and the majority of individuals in these studies had chronic PTSD.

Bonne and colleagues (Bonne et al., 2001) conducted one of the studies that failed to detect hippocampal volume reduction in association with PTSD. They completed a prospective longitudinal study of adults who experienced acute traumas that required treatment at a hospital emergency room and scanned participants within 1 week of the acute trauma and again 6 months later. Ten of the 37 participants included in the study had developed PTSD at follow-up. The hippocampal volumes of participants who developed PTSD and of those who did not were comparable at baseline and at the 6-month follow-up. These findings suggest that reduced hippocampal volume may be a marker of chronicity and not evident in the early stages of the disease process. Although the inclusion of a normal control comparison group in the study by Bonne and colleagues (Bonne et al., 2001) would have provided greater support for this proposition, as discussed later, findings of studies conducted with pediatric samples are consistent with this view (Carrion et al., 2001; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; De Bellis et al., 1999; De Bellis et al., 2002). In addition, in neuroimaging studies of adults with MDD, hippocampal volume reductions are significantly more common in adult depressed individuals with recurrent episodes of disorder than in individuals with single episodes of MDD (Bremner, Narayan, et al., 2000; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Vakili et al., 2000), with degree of hippocampal atrophy found to correlate significantly with lifetime duration of depressive illness (Sheline et al., 1996).

Although the failure to detect hippocampal volume differences in the study by Bonne and colleagues (Bonne et al., 2001) may be due to differences in the chronicity of PTSD symptoms, it may also be due to differences in the comorbid diagnostic profile of the participants. The participants included in the study by Bonne and colleagues had no history of alcohol abuse or dependence (Bonne et al., 2001), in sharp contrast to the studies that reported hippocampal volume reduction in association with PTSD. In one of the other studies that failed to report reduced hippocampal volume, although lifetime diagnoses were not reported, patients with PTSD and controls had consumed a comparable amount of liquor during the previous year (Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002). In another study that failed to detect hippocampal volume differences between individuals and controls (Schuff et al., 2001), all individuals with a history of alcohol dependence were required to have been abstinent for 5 or more years for inclusion in the study. Although six of the seven studies that reported reduced hippocampal volume in individuals with PTSD excluded individuals with current alcohol abuse and/or utilized statistical methods to control for lifetime alcohol use (Bremner et al., 1995; Bremner, Randall, et al., 1997; Gurvits et al., 1996; Stein et al., 1997; Villarreal et al., 2002; Vythilingam et al., 2002), the possibility that hippocampal volume reductions in patients with PTSD are related to alcohol use history cannot be entirely ruled out (Agartz, Momenan, Rawlings, Kerich, & Hommer, 1999; Beresford et al., 1999; De Bellis et al., 2000; Laakso et al., 2000).

The other neuroimaging study that failed to detect hippocampal volume differences between individuals and controls was conducted by Gilbertson and colleagues (Gilbertson et al., 2002). These investigators conducted a study with 35 identical twin pairs who were discordant for combat exposure. Twelve of the combat-exposed twins developed PTSD, 23 did not. The twins and their co-twins who had not been exposed to combat were scanned. Combat-exposed twins with PTSD *and* their unexposed co-twins were found to have smaller hippocampal volumes than combat-exposed twins without PTSD and their unexposed co-twins. Given that the identical twins who were not exposed to combat had hippocampal volumes that were comparable to those of their combat-exposed co-twins who developed PTSD and had significantly smaller hippocampi than combat-exposed men who did not develop PTSD, the authors concluded that the reduced hippocampal volume represented a preexisting, inherent vulnerability factor, rather than being a consequence of trauma exposure. This interpretation has to be accepted with caution, however, as the combat-exposed veterans who developed PTSD and their combat-unexposed co-twins were significantly more likely to have a history of alcohol dependence than the combat-exposed veterans who did not develop PTSD and their combat unexposed co-twins (alcohol dependence: Ex+PTSD/Ex-co-twin: 82% and 47% vs. Ex+noPTSD/Ex-co-twin: 43% and 30%). Childhood histories of sexual and physical abuse were also higher in the combat-exposed veterans who developed PTSD and in their combat-unexposed co-twins than in the other twin pairs (child abuse: Ex+PTSD/Ex-co-twin: 29% and 24% vs. Ex+NoPTSD/ex-co-twin: 13% and 9%).

In contrast to the findings reported by Gilbertson and colleagues (2002), in a yet-to-be-published study of dizygotic twin pairs discordant for combat exposure and PTSD diagnosis, combat veterans with PTSD were found to have significantly smaller hippocampal volumes than their dizygotic twins without combat exposure or PTSD (Bremner et al., 2001). Analyses of identical-twin-pair data collected as part of this study are currently underway (Bremner, personal communication, May, 2003), but the preliminary results do not appear to support the conclusions of Gilbertson and colleagues.

Alternatively, in one preclinical study of paternal half-sibling primates raised apart and randomized to various postnatal conditions, estimated heritability for hippocampal size was as high as 54% (Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001). This finding is consistent with twin (Kendler et al., 1995; Xian et al., 2000) and family (Davidson, Tupler, Wilson, & Connor, 1998; Reich, Lyons, & Cai, 1996) studies that suggest a genetic liability for exposure to trauma and the development of PTSD, a liability that is shared in part with the genetic risk for the development of MDD and alcohol and substance abuse disorders. It is likely that future neuroimaging studies that incorporate genetic and environmental measures will be most informative in unraveling the pathogenesis of PTSD.

Using the existing databases, it is impossible to definitely determine whether reductions in hippocampal volume in individuals with PTSD are due to predisposing factors, to the stress associated with the precipitating trauma, to altered capacity of the hippocampus to respond to subsequent neuronal assaults, to PTSD symptom persistence, to recurrent depression, or to alcohol consumption (Sapolsky, 2000). Although PTSD, MDD, and alcohol dependence are highly comorbid diagnoses, in most cases the PTSD predates the onset of these other disorders (Breslau et al., 1997; Goldenberg, Mueller, & Fierman, 1995; Kessler et al., 1995). Additional longitudinal studies of individuals with PTSD that start early in the course of the disorder will help to clarify these issues.

MAGNETIC RESONANCE SPECTROSCOPY STUDIES IN ADULTS WITH PTSD

Table 13.2 depicts the methods and results of magnetic resonance spectroscopy (MRS) studies conducted in adults with PTSD. The studies by Villerreal and colleagues (Villarreal et al., 2002) and by Schuff and colleagues (Schuff et al., 2001) included in the table are the same studies cited in the structural neuroimaging section. Although Schuff and colleagues (Schuff et al., 2001) failed to detect structural changes in hippocampal volume in individuals with PTSD, consistent with the other investigators using MRS, neurochemical differences were reported in this region. Specifically, in all three studies using MRS, individuals with PTSD were found to have reduced *N*-acetyl-L-aspartic acid (NAA) and creatine in the hippocampus region when compared with controls (Freeman, Cardwell, Karson, & Komoroski, 1998; Schuff et al., 2001; Villarreal et al., 2002). NAA reduction is typically interpreted as an indication of neuronal loss or damage (De Stefano, Matthews, & Arnold, 1995), with associated loss in neuron number, density, or neuronal metabolism (Birken & Oldendorf, 1989). Creatine reductions are suggestive of decreases in high-

TABLE 13.2. Magnetic Resonance Spectroscopy Studies in Adults with PTSD

Citation	Sample	Trauma	Method	Results
Freeman et al. (1998)	21 PTSD (100% M) 8 NC	Combat	MRS (1.5 T)	PTSD < TC NAA/Cr in medial temporal lobe (right) PTSD < TC Choline/Cr in medial temporal lobe (left)
Schuff et al. (2001)	18 PTSD (100% M) 19 NC	Combat	MRS (1.5 T)	PTSD < NC NAA hippocampus (left, right) PTSD < NC Cr hippocampus (right)
Villarreal et al. (2002)	8 PTSD (25% M) 5 NC	Mixed[a]	MRS (1.5 T)	PTSD < NC NAA hippocampus (left, trend) PTSD < NC Cr hippocampus (left, trend) PTSD < NC Cr occipital (left, right)

NOTES. PTSD, posttraumatic stress disorder; NC, normal control; M, male; MRS, magnetic resonance spectroscopy; NAA, *N*-acetyl-L-aspartic acid; Cr, creatine; T, tesla.
[a] Traumas included child sexual and physical abuse, assault, combat, and witnessing son's death in a fire.

energy phosphate metabolism (Urenjak, Williams, Giadian, & Noble, 1993). These MRS studies are consistent with the results of the structural neuroimaging studies and further suggest a role for the hippocampus in the pathophysiology of PTSD.

Because the individuals included in each of the MRS studies had chronic PTSD and because high rates of lifetime MDD and alcohol dependence were reported in each of the samples, it is impossible to determine whether these neurochemical alterations are predisposing factors for PTSD, are primary disturbances associated with illness onset, or are secondary changes resulting from symptom persistence or the development of co-occurring disorders. Further longitudinal research in this area is warranted as well.

EXPOSURE TO TRAUMATIC STIMULI DURING FUNCTIONAL NEUROIMAGING STUDIES IN ADULTS WITH PTSD

Twelve studies have utilized functional neuroimaging approaches to compare the neural correlates associated with exposure to traumatic stimuli in individuals with PTSD and in trauma controls (Bremner, 1999; Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Hendler, Rotshtein, & Hadar, 2001; Lanius et al., 2002; Lanius et al., 2001; Lanius et al., 2003; Liberzon et al., 1999; Shin et al., 1997a, 1997b, 1999; Shin et al., 2001; Zubieta et al., 1999). These studies are outlined in Table 13.3. The methodologies utilized in these studies vary considerably. Four studies employed positron emission tomography (PET), three studies used single photon emission computerized tomography (SPECT), and five studies used functional magnetic resonance imagining

TABLE 13.3. Exposure to Traumatic Stimuli during Functional Neuroimaging Studies in Adults with PTSD

Citation	Sample	Trauma	Method	Results[a]
Shin et al. (1997a)	7 PTSD (100% M) 7 TC	Combat	PET—oxygen-15-labeled CO_2 with exposure to neutral, negative, and combat pictures	Different patterns of rCBF changes reported in PTSD and TC participants in each of the conditions No group × condition interactions significant
Shin et al. (1997b)	8 PTSD (100% F) 7 TC	Child sexual abuse	PET—oxygen 15-labeled CO_2 with exposure to traumatic, neutral, and teeth-clenching conditions	Different patterns of rCBF changes reported in PTSD and TC participants in each of the conditions No statistical comparisons between the groups reported
Bremner, Staib, et al. (1999)	10 PTSD (100% M) 10 TC	Combat	PET—oxygen 15-labeled H_2O with combat and neutral slides and combat and neutral sounds	PTSD > TC change rCBF L. inferior parietal (40), R. parahippocampus, R. cerebellum/pons, mid cingulate (23), L. motor cortex (6) during exposure to combat stimuli PTSD < TC change rCBF medial PFC (25), L/R middle temporal gyrus (21, 39), L. thalamus during exposure to combat stimuli
Bremner, Narayan, et al. (1999)	10 PTSD (100% F) 12 TC	Child sexual abuse	PET—oxygen 15-labeled H_2O with traumatic and neutral scripts	PTSD > TC change rCBF L/R superior frontal gyrus (9), L. middle frontal gyrus (6), L/R posterior cingulate (24, 31), L. motor gyrus (4, 6), L. superior temporal gyrus (22) PTSD < TC change rCBF cerebellum, L/R middle occipital gyrus (19), R. supramarginal gyrus (40), R. sensory cortex (1,2), R. inferior frontal gyrus (44), subcallosal gyrus (25), anteromedial frontal gyrus (11), R. fusiform gyrus and inferior temporal gyrus (20), R. hippocampus during traumatic scripts
Liberzon et al. (1999)	14 PTSD (100% M) 11 TC 14 NC	Combat	SPECT—Tc-99m HMPAO with combat sounds and white noise	PTSD > TC = NC amygdala, nucleus accumbens
Shin et al. (1999)	8 PTSD (100% F) 8 TC	Child sexual abuse	PET—oxygen 15-labeled CO_2 with traumatic and neutral scripts	PTSD > TC change rCBF orbitofrontal cortex, anterior temporal poles during traumatic scripts condition

				PTSD < TC change in rCBF anterior and posterior cingulate gyrus, superior and middle frontal gyrus (9, 10, 46), inferior frontal gyrus, superior and middle temporal gyrus, parahippocampal gyrus, inferior parietal lobe during traumatic script
Zubieta et al. (1999)	12 PTSD (100% M) 11 TC 12 NC	Combat	SPECT—Tc-99m HMPAO with combat sounds and white noise	PTSD > TC = NC change rCBF medial PFC (9,10) during combat sounds condition
Lanius et al. (2001)	9 PTSD 9 TC	Child Abuse	fMRI (4.0 T) with traumatic scripts and baseline	PTSD < TC activation L/R thalamus, L/R medial frontal gyrus (10,11), L/R anterior cingulate gyrus (32), R. occipital lobe during traumatic memory
Shin et al. (2001)	8 PTSD (100% M) 8 TC	Combat	fMRI (1.5 T) emotional counting Stroop with combat, generally negative, and neutral words	PTSD > TC R/L anterior insular cortex PTSD < TC R. posterior insular cortex during combat compared with neutral
Hendler et al. (2001)	9 PTSD (100% M) 10 TC	Combat	fMRI (1.5 T) with repeat presentation of combat and neutral pictures	PTSD > TC lateral occipital complex activation to repeat presentations of combat pictures (trend)
Lanius et al. (2002)	7 PTSD (100% F) 10 TC	Child sexual abuse	fMRI (4.0 T) with traumatic scripts and baseline	PTSD > TC superior and middle temporal gyri (38, 39), inferior frontal gyrus (47), occipital lobe (19), parietal lobe precuneus (7), medial frontal gyrus (10), medial cortex (9), and anterior cingulate gyrus (24, 32) PTSD < TC L. parahippocampal gyrus (35), middle frontal gyrus (8), superior temporal gyrus (41,13)
Lanius et al. (2003)	10 PTSD 10 TC	Mixed[b]	fMRI (4.0 T) with baseline and scripts of traumatic, neutral, sad (unrelated to trauma), and anxious (unrelated to trauma) memories	PTSD < TC L/R thalamus, L/R anterior cingulate (24,32) all three mood states PTSD < TC also in the L.superior frotal gyrus (10), L/R inferior frontal gyrus (47,11), parietal lobe—precuneus (7) during traumatic scripts

Notes. PTSD, posttraumatic stress disorder; TC, trauma control; NC, normal control; M, male; F, female; PET, positron emission tomography; SPECT, single photon emission computerized tomography; Tc-99mHMPAO, 99m-technetrium hexamthyl-propyl-amine-oxime; fMRI, functional magnetic resonance imaging; CO_2, carbon dioxide; H_2O, water; rCBF, regional cerebral blood flow; L, left; R, right; PFC, prefrontal cortex; T, tesla.

[a] Numbers in parentheses are Brodmann's areas.

[b] Traumas included child sexual abuse, rape, and motor vehicle accidents.

(fMRI) techniques. Unlike the studies using structural MRI or MRS methodology, most of these studies did not include normal controls but rather trauma controls—individuals with similar traumatic experiences who do not meet criteria for current PTSD. Stimuli included exposure to traumatic and neutral pictures, sounds, single words, or scripts. In some studies, the activation to traumatic stimuli was contrasted with activation to neutral stimuli; in other studies, the activation to traumatic stimuli was compared with a resting baseline.

Table 13.4 summarizes the results of the 12 functional neuroimaging studies that used trauma-exposure paradigms. These studies do not present a coherent picture of the neural correlates associated with exposure to traumatic stimuli. Table 13.4 depicts: (1) the brain regions that were reported to have significantly different activation patters in individuals with PTSD and trauma controls; (2) associated Brodmann's areas, when reported by investigators; (3) the number of studies showing greater activation in patients with PTSD in each area; and (4) the number of studies showing reduced activation in patients with PTSD relative to trauma controls.

Across the 12 studies, 20 different brain regions were identified that distinguished individuals with PTSD from trauma controls, but no brain regions were consistently implicated. The best-replicated finding was increased activation in the motor cortex, with this finding detected in one-third of all studies and likely suggestive of hand clenching in response to traumatic stimuli exposure. Contradictory findings were reported in the majority of other brain regions cited across the different studies. Although altered functioning in regions involved in emotional processing is implicated in the majority of studies, no consistent pattern of findings is evident across the studies. In fact, different patterns of activation have been reported even in studies using the same neuroimaging paradigms (Lanius et al., 2002; Lanius et al., 2001; Lanius et al., 2003; Liberzon et al., 1999; Zubieta et al., 1999). Given variations in neuroimaging methodology and differences in the clinical characteristics of patients with PTSD and trauma controls, it is difficult to draw conclusions from this collection of studies.

ADDITIONAL NEUROIMAGING PARADIGMS IN ADULTS WITH PTSD

Resting Regional Blood Flow

Two studies have been conducted that compare resting regional blood flow in individuals with PTSD and normal controls (Lucey et al., 1997; Sachinvala, Kling, Suffin, Lake, & Cohen, 2000). Both studies utilized SPECT with 99m-technetrium hexamethyl-propyl-amine-oxime (Tc-99HMPAO). One study reported decreased regional blood flow in individuals with PTSD in the superior frontal lobe and caudate (Lucey et al., 1997), and the other study reported increased regional cerebral blood flow in the caudate, right putamen, orbital

TABLE 13.4. Summary of Results of 12 Studies Using Functional Neuroimaging Methods and Exposure to Traumatic Stimuli

Brodmann's area	Brain regions	Number of studies PTSD > TC	Number of studies PTSD < TC
Frontal lobe			
1,2	Sensory cortex		1
6	Motor cortex, middle frontal gyrus,	3	
4,6	motor gyrus, precentral lobule	1	
9	Superior frontal gyrus, medial cortex	2	
10	Superior frontal gyrus		1
8	Middle frontal gyrus		1
9,10,46	Superior and middle frontal gyrus		1
9,10	Medial PFC, medial cortex	2	2
10,11	Medial frontal gyrus		1
11	Anterior medial frontal gyrus		1
	Orbitofrontal	1	
47,11	Inferior frontal gyrus	1	1
44	Inferior frontal		1
Parietal lobe			
40	Inferior parietal, supramarginal gyrus	2	2
	Cuneus	1	
7	Parietal lobe, precuneus	1	1
Temporal lobe			
21,39	Middle temporal gyrus		1
38,39	Superior and middle temporal gyrus		1
41,13	Superior temporal gyrus		1
22	Superior temporal gyrus	2	
20	Fusiform gyrus, inferior temporal gyrus	1	1
	Anterior temporal pole	1	
Occipital lobe, brain stem, cerebellum			
19	Middle occipital gyrus		1
	Occipital lobe	1	1
	Cerebellum	1	1
	Pons	1	1
Subcortical brain regions			
24,32	Anterior cingulate	1	3
	Dorsal anterior cingulate	1	
23	Midcingulate	1	
24,31	Posterior cingulate	2	1
	Thalamus	1	3
	Insular cortex	1	
	Parahippocampus	1	2
	Hippocampus		1
	Amygdala	1	
	Nucleus accumbens	1	

Note. PFC, prefrontal cortex.

cortex, anterior and posterior cingulate, right temporal and parietal regions, and hippocampal regions (Sachinvala et al., 2000). There is no consensus definition of the resting state; it is difficult to control, and it may vary unpredictably (Gusnard & Raichle, 2001). Improved investigation of resting-state blood flow will require human and animal investigation with direct recording of neural activity during resting states to better understand normal resting state physiology and development of theoretical approaches to understand coherence and stability of baseline measures (Gusnard & Raichle, 2001). At present, interpretation of resting-state data is imprecise.

Functional Neuroimaging with an Attention Task

Semple and colleagues conducted three studies using PET in which individuals and controls were scanned during rest and during the performance of an auditory continuous-performance attention task (Semple et al., 1993; Semple et al., 1996; Semple et al., 2000). Participants were presented with a series of 500-Hz tones and instructed to press a button when a target tone was heard. In the first investigation, 6 individuals with PTSD and substance abuse histories and 7 normal controls were studied, and no regional blood flow differences were reported between the two groups during the auditory attention task (Semple et al., 1993). In the second study with a cohort of 8 individuals with PTSD and substance abuse histories and 8 normal controls, individuals with PTSD made more errors than normal controls, and had increased right supramarginal gyrus blood flow (Semple et al., 1996). In the last study, with a cohort of 7 individuals with PTSD and substance abuse histories and 6 normal controls increased blood flow was reported in the PTSD group in the amygdala and left parahippocampal gyrus, and decreased blood flow was reported in the frontal cortex (Semple et al., 2000). Replication of these findings in larger samples, with and without substance abuse histories, is required to better understand the potential mechanisms underlying attention deficits in individuals with PTSD.

Functional Neuroimaging with Working Memory Tasks

Two studies used PET to study working memory in individuals with PTSD (Clark et al., 2003; Shaw et al., 2002). In both studies, participants were instructed to detect neutral target words presented in two colors under fixed and variable target conditions. In the fixed condition participants were to press a button when an a priori defined target word in a given color appeared (e.g., the word "bell" in blue). In the variable-target condition, a target was defined as a consecutive repeat of any word in the attended color. In both studies, patients with PTSD showed reduced activation in the dorsolateral prefrontal cortex when performing the variable-target working-memory portion of the task. Other regional activation differences between individuals and controls were not consistently reported in the two studies. The reduction in dorsolateral prefrontal cortex activation, however, suggests a decreased dependence on executive function in monitoring and manipulating working-memory content in individuals with PTSD.

Functional Neuroimaging with a Masked Faces Paradigm

In an fMRI task, photographic images of fearful, happy, and neutral facial expressions were presented, with fearful and happy expressions shown for 33 milliseconds (target), followed immediately by a 167-millisecond presentation of a neutral expression (mask). The task was administered to 8 Vietnam veterans with current PTSD and 8 veterans in a trauma control group (Rauch et al., 2000). When compared with trauma controls, individuals with PTSD had significantly greater amygdala response during exposure to the masked fearful faces than during exposure to the masked happy faces. No medial frontal activation was evident during this task administration (Rauch et al., 2000). These findings suggest that individuals with PTSD have exaggerated autonomic responses within the amygdala to threat or negative-emotion-related stimuli.

Neuroimaging with a Pharmacological Challenge Paradigm

Bremner and colleagues used PET and [^{18}F]fluorodeoxyglucose to measure brain metabolism in 10 Vietnam veterans with PTSD and 10 healthy age-matched controls following administration of yohimbine or placebo in a randomized, double-blind fashion (Bremner, Innis, et al., 1997). After yohimbine, an alpha-2 adrenergic antagonist, individuals with PTSD had decreased regional cerebral blood flow in the orbitofrontal, parietal, prefrontal, and temporal cortices when compared with normal controls. Yohimbine administration was also associated with anxiety symptoms in individuals, but not in controls. These findings suggest that patients with PTSD have increased norepinephrine (NE) release following yohimbine administration and increased central NE drive, consistent with predictions from preclinical studies of the effects of stress (Francis, Diorio, Liu, & Meaney, 1999; Ladd, Owens, & Nemeroff, 1996; Liu, Caldji, Sharma, Plotsky, & Meaney, 2000).

Receptor Binding Neuroimaging

Bremner and colleagues (Bremner, Innis, et al., 2000) used SPECT imaging with iomazenil to assess benzodiazepine binding in 13 individuals with Vietnam combat-related PTSD and 13 matched normal controls. Individuals with PTSD had reduced benzodiazepine binding in the prefrontal cortex (Brodmann's area 9), with individuals with PTSD showing a 41% reduction in distribution volume (the benzodiazepine receptor binding measure) in this area. No other regions showed receptor binding differences. The authors emphasized that the prefrontal cortex mediates several cognitive and behavioral processes that are relevant to PTSD, including inhibition of cognition, emotions, and behaviors. The reduction in benzodiazepine binding is also consistent with results of preclinical studies that suggest that early stress leads to decreased tone of the inhibitory gamma-aminobutyric acid/benzodiazepine (GABA/BZ) system (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Francis, Caldji, Champagne, Plotsky, & Meaney, 1999).

NEUROIMAGING STUDIES IN CHILDREN AND ADOLESCENTS WITH PTSD

Table 13.5 depicts the results of the neuroimaging studies conducted with children and adolescents with PTSD. There have been four structural neuroimaging studies to date (Carrion et al., 2001; De Bellis, Hall, et al., 2001; De Bellis et al., 1999; De Bellis et al., 2002), with one publication reporting repeat longitudinal assessments on a subset of the children who participated in an earlier investigation (De Bellis, Hall, et al., 2001). None of the studies detected evidence of hippocampal atrophy in children and adolescents with PTSD compared with controls (Carrion et al., 2001; De Bellis, Hall, et al., 2001; De Bellis et al., 1999; De Bellis et al., 2002). Group differences in NAA and creatine have not been examined in the hippocampus in pediatric samples (De Bellis, Keshavan, & Harenski, 2001).

Instead of hippocampal atrophy, the children and adolescents with PTSD were found to have smaller intracranial and cerebral volumes than normal controls (Carrion et al., 2001; De Bellis et al., 1999; De Bellis et al., 2002). Intracranial and cerebral volume group differences have not been examined consistently in adult studies, and group differences in whole brain volume are reported in only 1 of the 11 extant adult structural MRI studies (Fennema-Notestine et al., 2002). Two of the pediatric MRI studies also reported increased right, left, and total lateral ventricle volume (De Bellis et al., 1999; De Bellis et al., 2002), and one study reported reduced right frontal lobe volume (Carrion et al., 2001).

In addition, two published pediatric studies reported decreased area of the medial and posterior portions of the corpus callosum (De Bellis et al., 1999; De Bellis et al., 2002). Consistent with these reports, in a recent abstract, psychiatric inpatients with a history of maltreatment were likewise reported to have significant reduction in the medial and caudal portions of the corpus callosum when compared with psychiatric and healthy controls without a history of early child maltreatment (Teicher et al., 2000). Studies with adults have not obtained corpus callosum measurements.

To the best of our knowledge, there is only one published structural MRI study in prepubescent nonhuman primates subjected to early stress (Sanchez, Hearn, Do, Rilling, & Herndon, 1998). Most preclinical studies of early stress have examined the long-term impact of these experiences on brain development in *adult* animals. Interestingly, the study with the young primates also failed to find evidence of hippocampal atrophy. Instead, consistent with the

TABLE 13.5. Neuroimaging Studies in Children and Adolescents with PTSD

Citation	Sample	Lifetime diagnoses	Trauma	Method	Results
DeBellis et al. (1999)	44 PTSD 44 NC	45% MDD 0% ALC	Child abuse	Structural MRI (1.5 T), 1.5-mm contiguous slices	PTSD = NC hippocampus PTSD < NC intracranial volume, cerebral volume, corpus callosum (mid- and posterior areas 4–7) PTSD > NC lateral ventricles
Carrion et al. (2001)	12 PTSD 11 NC	13% MDD 0% ALC	Child abuse	Structural MRI (1.5 T), 1.5-mm contiguous slices	PTSD = NC hippocampus PTSD < NC intracranial volume, cerebral volume, R. frontal lobe Group differences in corpus callosum area not examined
DeBellis et al. (2002)	9 PTSD 9 NC	89% MDD 0% ALC	Child abuse	Structural MRI (1.5 T), 1.5-mm contiguous slices, 2 scans at 2-year interval	PTSD = NC cerebral volume, temporal lobe, amygdala, hippocampus at baseline and 2-year follow-up
DeBellis et al. (2003)	28 PTSD 66 NC	50% MDD 0% ALC	Child abuse	Structural MRI (1.5 T), 1.5-mm contiguous slices	PTSD = NC hippocampus PTSD < NC intracranial volume, cerebral volume, corpus callosum (mid- and posterior areas 4–7) PTSD > NC lateral ventricles
DeBellis et al. (2000)	11 PTSD 11 NC	55% MDD 0% ALC	Child abuse	MRS (1.5 T)	PTSD < NC NAA/Cr ratio anterior cingulate Group differences in hippocampus and other brain regions not reported

Note. PTSD, posttraumatic stress disorder; NC, normal control; MDD, major depressive disorder; MRI, magnetic resonance imaging; NAA, *N*-acetyl-L-aspartic acid; Cr, creatine; ALC, alcohol abuse; T, tesla.

child and adolescent studies described previously, the investigators reported reductions in the medial and caudal portions of the corpus callosum in the juvenile, nonhuman primates subjected to early stress (Sanchez et al., 1998).

The medial and caudal portions of the corpus callosum contain interhemispheric projections from the cingulate, posterior temporal–parietal sensory association cortices, superior temporal sulcus, retrosplenial cortex, insula, and parahippocampal structures (Pandya & Seltzer, 1986). Several of the regions with interhemispheric projections through the medial and caudal portions of the corpus callosum have direct connections with prefrontal cortical areas and are involved in circuits that mediate the processing of emotion and various memory functions—core disturbances observed in individuals with PTSD.

Given the prominence of corpus callosum alterations in children and adolescents with PTSD, our group has conducted a preliminary study using diffusion tensor imaging (DTI) in 8 maltreated children with PTSD and 7 normal controls (Kaufman et al., 2001). DTI can be used to assess the integrity of white matter tracts in the brain. Children with PTSD had significantly greater mean diffusivity in the medial and posterior region of the corpus callosum, a finding that is consistent with the possibility of reduced axonal pruning early in development. There were no group differences in fractional anisotropy, but the two groups were not matched on age, and fractional anisotropy correlated significantly with age ($r = .045$, $p < .05$). When the fractional anisotropy values of the three age- and gender-matched PTSD and control pairs were compared, the children with PTSD had a 23% reduction in fractional anisotropy values (range: 12–39%). This finding is consistent with the possibility of reduced myelination in children with PTSD compared with age-matched controls. We are currently in the process of expanding this pilot initiative to further investigate the role of the corpus callosum in the pathophysiology of PTSD. Corpus callosum assessments should be examined in adults and additional research conducted to examine interhemispheric processing in patients with PTSD.

SUMMARY OF PTSD NEUROIMAGING STUDIES

Reduced hippocampal volume has been reported in 7 of the 11 structural neuroimaging studies of adults with PTSD and in none of the 4 structural neuroimaging studies of children and adolescents with PTSD. In all the studies that reported reduced hippocampal volume, individuals had a chronic course of illness, and high rates of MDD and history of alcohol dependence were reported within the samples. At present, it is impossible to determine whether reductions in hippocampal volume in individuals with PTSD are due to predisposing factors, to the stress associated with the precipitating trauma, to altered capacity of the hippocampus to respond to subsequent neuronal assaults, to PTSD symptom persistence, to recurrent depression, or to alcohol consumption. It is our best guess that all these factors contribute. In addition, as discussed later, an understanding is emerging of developmental factors that appear to contribute to the failure to detect hippocampal volume changes in pediatric cohorts.

MRS studies in adults with PTSD have consistently reported reduced hippocampal NAA and creatine in patients compared with controls. Longitudinal studies are also required to determine whether these changes are primary or secondary to persistence of disorder or onset of additional comorbid psychiatric conditions.

Studies that examine neural correlates of exposure to traumatic stimuli implicate a role for brain regions involved in the processing of emotion in patients with PTSD, but given methodological variations, no coherent patterns of activation in response to traumatic stimuli have been reported across studies. Two studies using functional neuroimaging approaches reported that individuals with PTSD had reduced dorsolateral prefrontal cortex activation compared with controls when completing working memory tasks. Another study reported greater amygdala activation in patients with PTSD after exposure to masked fearful faces, and evidence of altered central norepinephrine and GABA functioning has also been demonstrated via pharmacological challenge and receptor-binding neuroimaging studies. Although some of these findings require replication, the emerging data suggest that core neurochemical systems and neuroanatamical structures involved in the stress response are altered in PTSD.

The corpus callosum findings reported in pediatric samples of patients with PTSD have not been examined in adults with PTSD. The parallel findings in children and adolescents and in prepubescent primates subjected to early stress, however, suggest a potential primary role for interhemispheric processing in the pathophysiology of PTSD and highlight the need for further study of brain connectivity more generally.

PRECLINICAL STUDIES RELEVANT TO UNDERSTANDING NEUROIMAGING FINDINGS

Comorbidity in Patients with PTSD

Preclinical studies suggest that maternal separation, early stress paradigms provide good models for studying the development of anxiety disorders, depression, and alcohol and substance use disorders (Charney, Grillon, & Bremner, 1998; Heim, Owens, Plotsky, & Nemeroff, 1997; Huot, Thrivikraman, Meaney, & Plotsky, 2001; Meaney, Brake, & Gratton, 2002). Maternal separation is associated with increased stress reactivity, decreased exploratory behavior in novel environments, decreased water consumption, and increased ethanol consumption in adult rats (Huot et al., 2001). In addition, early stress alters the development of the mesolimbic dopamine system, which has been proposed as a neurobiological mechanism by which these experiences infer a vulnerability for the development of substance abuse problems. Better understanding of the interrelationships among the systems affected by stress and the behaviors they subserve will provide additional insights into the mechanisms underlying the high rates of comorbidity among PTSD, MDD, and alcohol and substance use disorders.

Gene and Environment Interactions

Several studies have been conducted that suggest that gene and environment interactions are important in understanding the neurobiological effects of stress, with species with more intrinsic reactivity more responsive to the effects of environmental manipulations than species that are less intrinsically reactive (Anisman, Zaharia, Meaney, & Merali, 1998; Steimer, Escorihuela, Fernandez-Teruel, & Driscoll, 1998; Zaharia, Kulczycki, Shanks, Meaney, & Anisman, 1996). For example, in one study, primates with two different genetic variations of the serotonin transporter gene were reared by either peers or parents (Bennett et al., 2002). Animals with the heterozygous alleles who were peer reared had lower cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite, than heterozygous animals who were parent reared and than homozygous animals that were either parent or peer reared. Low CSF 5-HIAA is associated with depression, suicidality, and impulsive aggression—common symptoms observed in individuals with histories of early childhood trauma and/or a diagnosis of PTSD. The inclusion of genetic research approaches in future neuroimaging studies will be invaluable in unraveling the impact of environmental experiences and inherent vulnerability on the development of PTSD and its neural underpinnings. There is a growing appreciation of the role of genetics on the individual's response to trauma and of the influence of environment on the expression of critical genes activated in the stress response. Genes and environment are dynamic in their interactions, and better understanding of the nature of these interactions and their impact on brain development will help to identify novel therapeutic approaches to prevent and/or ameliorate the deleterious effects of extreme stress for vulnerable individuals.

Hippocampus

Preclinical studies of the effects of stress suggest a minimum of three mechanisms by which hippocampal atrophy may develop in individuals with PTSD: neuronal atrophy, neurotoxicity, and neurogenesis. Preclinical studies have found that 3 weeks of exposure to stress and/or stress levels of glucocorticoids can cause neuronal atrophy in the CA3 region of the hippocampus (Watanabe, Gould, & McEwen, 1992; Woolley, Gould, & McEwen, 1990). At this level, glucocorticoids produce a reversible decrease in number of apical dendritic branch points and length of apical dendrites of sufficient magnitude to impair hippocampal-dependent cognitive processes (Watanabe et al., 1992). More sustained stress and/or glucocorticoid exposure can lead to neurotoxicity—actual permanent loss of hippocampal neurons through binding of glutamate to N-methyl-D-aspartate (NMDA) receptors. Rats exposed to high concentrations of glucocorticoids for approximately 12 hours per day for 3 months experience a 20% loss of neurons specific to the CA3 region of the hippocampus (Sapolsky, Krey, & McEwen, 1985). Evidence of stress-induced neurotoxicity of cells in this region has been reported in nonhuman primates as well (Sapolsky, 1996; Uno et al., 1994). Reductions in hippocampal volume may also be affected by decreases in neurogenesis that result from decreased expression of brain-derived neurotrophic factor (BDNF) caused by elevated glucocorticoids (Gould & Cameron, 1996). The granule cells in the dentate gyrus of the hippocampus continue to proliferate into adulthood, and neurogenesis in this region is markedly reduced by stress.

Developmental Factors

Emerging findings suggest that multiple developmental factors may be relevant in understanding the absence of hippocampal findings in prepubescent primates subjected to early stress and in children and adolescents with PTSD. For example, there are age-dependent changes in sensitivity to some forms of NMDA receptor blockade: as in preclinical studies of neurotoxicity in corticolimbic regions, cell death has been reported to be minimal or absent prepuberty and reaching peak only in early adulthood (Farber et al., 1995). In addition, in another study, changes in BDNF and NMDA receptors were examined in rats subjected to maternal separation immediately following separation, during a later point in development before weaning, and again during adulthood (Roceri, Hendriks, Racagni, Ellenbroek, & Riva, 2002). As adults, when compared with control animals, rats subjected to early separation showed reduced BDNF baseline levels, smaller changes in BDNF after acute stress, and reduced NMDA receptor subunits in the hippocampus. No changes in BDNF or NMDA receptors were evident immediately following separation or at the other preweaning time point examined. Given these findings, it has been suggested that adverse events during brain maturation may modulate expression of molecular components involved in cellular plasticity within selected brain regions, potentially promoting an increased vulnerability to psychopathology, with some resulting brain changes not evident until later in development or adulthood. Alterations in interhemispheric connectivity may represent an additional mechanism by which early adversity may indicate a vulnerability to later psychopathology and promote additional brain changes observed in later in development.

Amygdala

Studies in animals suggest that the amygdala plays a critical role in the acquisition and elaboration of fear conditioning (Cahill, Weinberger, Roozendaal, & McGaugh, 1999; Davis, 1997). The amygdala is activated during stress by ascending catecholamine neurons originating in the brainstem and by cortical association neurons involved in processing stressful stimuli via direct and indirect medial and orbital prefrontal cortical connections (Lopez, Akil, & Watson, 1999). Neurons of the central nucleus of the amygdala respond positively to glucocorticoids and activate the locus coerelus–norepinephrine (NE) component of the stress system (Lopez et al., 1999). Maternal deprivation is associated with increased amygdala stress responsiveness (Menzaghi, Heinrichs, Pich, Weiss, & Koob, 1993). The preliminary results reported in patients with PTSD are consistent with these preclinical findings.

Prefrontal Cortex

There is growing appreciation of the role of cortical inputs in the stress response (Lopez et al., 1999), with medial prefrontal cortex (PFC), anterior cingulate, and orbital PFC currently understood to play an important role in relaying information from primary sensory and association cortices to subcortical structures involved in the stress response. Medial and orbital PFC are reciprocally interconnected, and each has indirect connections with the hypothalamus and amygdala via inputs to the periaqueductal gray and parabrachial nucleus (An, Bandler, Ongur, & Price, 1998; Krout, Jansen, & Loewy, 1998). The medial and orbital prefrontal cortices also provide direct inputs to the hypothalamus and are reciprocally connected with the amygdala (Ongur, An, & Price, 1998). These prefrontal regions appear to be critical in restraining the acute stress response and facilitating negative feedback inhibition of the stress system (Herman & Cullinan, 1997). Early maternal separation and social isolation have been found to alter the development of efferents to frontal areas believed to be analogous to the medial prefrontal cortex (mPFC) in humans and other primates (Braun, Lange, Metzger, & Poeggel, 2000; Poeggel et al., 1999), reducing negative feedback in the stress response. The preliminary results reported in patients with PTSD are also consistent with these preclinical findings.

Neurochemical Systems

Extensive research has been conducted examining the neurobiological effects of early stress, with these experiences associated with increased central corticotropin releasing hormone and NE drive in adulthood (Francis, Diorio, et al., 1999; Ladd et al., 1996; Liu, Caldji, et al., 2000), and decreased tone of the inhibitory gamma-aminobutyric acid–benzodiazepine (GABA–BZ) system (Caldji et al., 2000; Francis, Caldji, et al., 1999). Emerging findings in patients with PTSD are also consistent with these preclincal findings.

Neuroplasticity

Evidence is emerging that the long-term neurobiological consequences of early stress evident in vulnerable individuals need not be permanent. Cross-fostering experiments in rats subjected to early maternal deprivation suggest that provision of optimal parenting subsequent to the early separation can prevent and/or reverse many of the long-term changes associated with early stress (Anisman et al., 1998; Francis, Diorio, et al., 1999; Liu, Diorio, Day, Francis, & Meaney, 2000). In addition, pharmacological interventions may likewise prevent and/or reverse the neurobiological changes associated with early stress (Magarinos, Deslandes, & McEwen, 1999; McEwen et al., 1997; Plotsky, personal communciation, 1999). Consistent with these preclinical studies, propranolol, a beta-adrenergic blocker, has preliminarily been found to prevent the onset of PTSD in adults when administered after an acute trauma (Pitman et al., 2002), and long-term treatment with a paroxetine, a selective serotonin reuptake inhibitor (SSRI), in addition to promoting symptom reduction, has been found to reverse hippocampal atrophy and memory deficits in patients with PTSD (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003).

DIRECTIONS FOR FUTURE RESEARCH

1. The majority of preclinical (e.g. animal) studies investigating the impact of early stress have examined the impact of these experiences on the neurobiology of *adult* animals. More developmental studies of the effects of stress are needed to determine which biological alterations are evident immediately following early stress, which emerge at different developmental stages (e.g. prepuberal, postpubertal, adulthood), and what mechanisms are responsible for the emergence of neurobiological alterations at subsequent points in time.

2. Preclinical studies are needed to identify the mechanisms that promote growth changes in the corpus callosum in juvenile cohorts subjected to early stress and to determine whether corpus callosum atrophy is associated with changes in axon number and/or reductions in myelination.

3. Additional exploration of preclinical studies of stress that model the onset of depression- and anxiety-like behaviors together with the onset of substance use disorders are needed to better understand the mechanisms behind the frequent co-occurrence of PTSD, MDD, and alcohol and/or substance use disorders.

4. Additional longitudinal studies of children, adolescents, and adults immediately following trauma and early in the disease process will help to delineate the primary neuroanatomical and neurochemical disturbances associated with PTSD onset from those that emerge as a consequence of development, PTSD persistence, and/or the onset of co-occurring other psychiatric disorders.

5. Additional studies using standard functional neuroimaging paradigms that can be applied to patients and normal controls are needed. Emphasis should be on the use of paradigms that utilize neural networks hypothesized to be altered in patients with PTSD, such as working memory, affect process-

ing, interhemispheric transfer, attention, startle, and fear-conditioning paradigms.

6. Neuroimaging studies examining central NE and gamma-aminobutyric acid (GABA) should be replicated, and studies examining central corticotropin releasing hormone conducted.

7. Neuoimaging studies should be conducted using candidate gene, twin, sibling-pair, and/or family study designs to better understand the interactions between inherent factors and experiences of extreme stress in the onset of PTSD and the neurobiological alterations associated with the disorder.

8. Given emerging findings that suggest that the quality of the subsequent caregiving environment and some pharmacological interventions can ameliorate and/or reverse neurobiological alterations associated with early stress, additional longitudinal repeat neuroimaging assessments before and after psychosocial (e.g. adoption), and pharmacological interventions are warranted to evaluate neuroplasticity in patients with PTSD.

CONCLUSIONS

PTSD is a common and often unremitting disorder. Preclinical studies suggest that early and/or extreme stress is associated with an increase in central CRH and NE drive, reduced function in the inhibitory GABA/BZ system, and long-term changes in hippocampus, amygdala, and prefrontal regions that are critical in integrating the stress response. The extant neuroimaging data in patients with PTSD support the role of these neurochemical systems and neuroanatomical structures in the pathophysiology of PTSD. The emerging preclinical and clinical literature, however, also highlight the importance of genetic, subsequent environment, comorbid clinical, and developmental factors in understanding the long-term neurobiological sequelae of extreme stress. Careful consideration of these additional factors in future neuroimaging studies will increase our understanding of the neural underpinnings of PTSD, help to identify factors that increase and decrease the likelihood of long-term neurobiological alterations in response to stress, and suggest novel preventive and therapeutic intervention approaches for individuals with PTSD.

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